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Appeal Brief

Applicant(s)	Turner et al.
Application #	09/691,343
Date Filed	Oct 18, 2000
Title	Novel Human Proteins and Polynucleotides Encoding the Same
Attorney Docket #	LEX-0070-USA
Group Art Unit	1647
Examiner	R. DeBerry

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Turner Jr. *et al.*		
Serial No.:	09/691,343	Group Art Unit:	1647
Filed:	10/18/2000	Examiner:	R. DeBerry
For:	Novel Human Proteins and Polynucleotides Encoding the Same	Attorney Docket No.:	LEX-0070-USA

APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Assistant Commissioner for Patents
Alexandria, VA 22313

APPEAL BRIEF

Sir:

Appellants hereby submit an original and two copies of this Appeal Brief to the Board of Patent Appeals and Interferences ("the Board") in response to the Final Office Action mailed on June 16, 2003. The Notice of Appeal was timely submitted on October 16, 2003, and was received in the Patent and Trademark Office ("the Office") on October 20, 2003. This Appeal Brief is timely submitted in light of the concurrently filed Petition for an Extension of Time of two months to and including February 20, 2004, and authorization to deduct the fee as required under 37 C.F.R. § 1.17(a)(2) from Appellants' Representatives' deposit account. The Commissioner is also authorized to charge the fee for filing this Appeal Brief ($165.00), as required under 37 C.F.R. § 1.17(c), to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

Appellants believe no fees in addition to the fee for filing the Appeal Brief and the fee for the extension of time are due in connection with this Appeal Brief. However, should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason related to this communication, the Commissioner is authorized to charge any underpayment or credit any overpayment to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

I. REAL PARTY IN INTEREST

The real party in interest is the Assignee, Lexicon Genetics Incorporated, 8800 Technology Forest Place, The Woodlands, Texas, 77381.

II. RELATED APPEALS AND INTERFERENCES

Appellants know of no related appeals or interferences that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF THE CLAIMS

The present application was filed on October 18, 2000, claiming the benefit of U.S. Provisional Application Numbers 60/160,106 and 60/162,547, which were filed on October 18, 1999

and October 29, 1999, respectively, and included original claims 1-6. A Restriction and Election Requirement was issued on July 22, 2002, separating the original claims into three separate and distinct inventions. In a response to the Restriction and Election Requirement submitted to the Office on August 22, 2002, Appellants elected without traverse the claims of the Group III invention (original claims 4-6) for prosecution on the merits, cancelled claims 1-3 without prejudice and without disclaimer as drawn to non-elected inventions, amended claim 5 to further improve its clarity, and added new claims 7 and 8.

A First Official Action on the merits ("the First Action") was issued on November 6, 2002, in which claims 4-8 were rejected under 35 U.S.C. § 101 as allegedly lacking a patentable utility, claims 4-8 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, claims 4, 7 and 8 were apparently rejected under 35 U.S.C. § 112, first paragraph, as allegedly not providing enablement for "fragments of polynucleotides" (the First Action at page 6), claims 4 and 5 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, and claim 5 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. In a response to the First Action submitted to the Office on March 6, 2003 ("Response to the First Action"), Appellants amended claim 5 to even further improve its clarity, added new claims 9-11, and addressed the various rejections of claims 4-8.

A Second and Final Official Action ("the Final Action") was issued on June 16, 2003, indicating that the rejection of claim 5 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, and claim 2 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite, had been overcome by the amendments and remarks submitted in the Response to the First Action, but maintaining the rejection of claims 4-8 (and newly added claims 9-11) under 35 U.S.C. § 101 as allegedly lacking a patentable utility, claims 4-8 (and newly added claims 9-11) under 35 U.S.C. § 112, first paragraph, as allegedly unusable by the skilled artisan due to the alleged

lack of patentable utility, claims 4, 7 and 8 under 35 U.S.C. § 112, first paragraph, as allegedly not enabled, and claim 4 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In a response to the Final Action submitted to the Office on October 16, 2003 ("Response to the Final Action"), Appellants addressed the various rejections of claims 4-11.

An Advisory Action ("the Advisory Action") was mailed on December 17, 2003, maintaining the rejection of claims 4-11 under 35 U.S.C. § 101 as allegedly lacking a patentable utility, claims 4-11 under 35 U.S.C. § 112, first paragraph, as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, claims 4, 7 and 8 under 35 U.S.C. § 112, first paragraph, as allegedly not enabled, and claim 4 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Therefore, claims 4-11 are the subject of this appeal. A copy of the appealed claims are included below in the Appendix (Section IX).

IV. STATUS OF THE AMENDMENTS

As no amendments subsequent to the Final Action have been filed, Appellants believe that no outstanding amendments exist.

V. SUMMARY OF THE INVENTION

The present invention relates to Appellants' discovery and identification of novel human polynucleotide sequences that encode a novel member of the platelet-derived growth factor/VEGF family (specification from page 2, line 34 to page 3, line 1).

The presently claimed polynucleotide sequences were compiled from clustered human gene trapped sequences and ESTs (specification at page 7, lines 29-30). A coding single nucleotide polymorphism was identified in the claimed sequence - specifically, an A/T polymorphism at position 598 of SEQ ID NO:6, which can lead to an isoleucine or valine residue at amino acid position 200 of SEQ ID NO:7 (specification from page 7, line 37 to page 8, line 2).

The specification details a number of uses for the presently claimed polynucleotide sequences, including in diagnostic assays such as forensic analysis (see, for example, the specification at page 10, line 35), in determining the genomic structure (see, for example, the specification at page 3, lines 9-13), and in assessing gene expression patterns, particularly using a high throughput "chip" format (see, for example, page 5, lines 4-7, in priority document 60/162,547, which was incorporated in its entirety by reference into the present specification as originally filed).

VI. ISSUES ON APPEAL

1. Do claims 4-11 lack a patentable utility?
2. Are claims 4-11 unusable by a skilled artisan due to a lack of patentable utility?
3. Are claims 4, 7 and 8 enabled?
4. Does claim 4 lack sufficient written description?

VII. GROUPING OF THE CLAIMS

For the purposes of the outstanding rejections under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, associated with the utility rejection, the claims will stand or fall together. For the purpose of the outstanding rejection under 35 U.S.C. § 112, first paragraph, associated with enablement, claims 4, 7 and 8 will stand or fall together. For the purpose of the outstanding rejection under 35 U.S.C. § 112, first paragraph, associated with written description, claim 4 will stand or fall alone.

VIII. ARGUMENT

A. Do Claims 4-11 Lack a Patentable Utility?

The Final Action first rejects claims 4-11 under 35 U.S.C. § 101, as allegedly lacking a patentable utility due to not being supported by either a specific and substantial or a well-established utility.

Appellants pointed out both in the Response to the First Action and the Response to the Final Action that the present nucleic acid sequences clearly have utility in diagnostic assays such as forensic analysis, as described in the specification as originally filed (see, for example, page 10,

line 35). As described in the specification from page 7, line 37 to page 8, line 2, the presently claimed sequence defines a coding single nucleotide polymorphisms - specifically, an A/T polymorphism at position 598 of SEQ ID NO:6, which can lead to an isoleucine or valine residue at amino acid position 200 of SEQ ID NO:7. As polymorphisms such as this are the basis for forensic analysis, which in undoubtedly a "real world" utility, the presently claimed sequence must in itself be useful.

In the Final Action, the Examiner questioned this asserted utility, stating "it does not mean that the change in amino acid will affect activity or cause a disease or condition" (the Final Action at page 3). The Examiner reiterates this position in the Advisory Action, stating that "(a) way of identifying a population of people which (*sic*) carry a particular polymorphism, wherein the polymorphism itself does not cause a disease or condition (i.e. (*sic*) lacks a substantial utility) fails to have a 'real world use'" (the Advisory Action at page 2). Naturally occurring genetic polymorphisms such as that described in the present specification are both the basis of, and critical to, *inter alia*, forensic genetic analysis intended to resolve issues of, for example, identity or paternity. Forensic analysis based on identified polymorphisms such as that identified by Appellants is used to positively identify or rule out suspects in many criminal cases, and in identifying human remains. Paternity determination is based on identified polymorphisms such as that identified by Appellants to positively identify or rule out individuals suspected of fathering a particular child. Therefore, Appellants find the Examiner's position particularly difficult to comprehend. What could be possibly be more substantial and real world than the loss of an individual's freedom or life through incarceration? What could be possibly be more substantial and real world than the positive identification of human remains? What could be possibly be more substantial and real world than the impact, both economic and emotional, that the results of a paternity analysis has on the individuals directly and indirectly involved? These are all well known and generally accepted uses of identified polymorphisms such as the polymorphism identified by Appellants. Without such identified polymorphisms, the skilled artisan would not be able to carry out such forensic or paternal analyses. Thus, the Examiner's argument in no way supports the allegation that the presently claimed sequence lacks a patentable utility.

Far from supporting the allegation that the presently claimed sequence lacks a patentable

utility, these arguments instead merely reflect how **completely** misinformed the Examiner is with **forensic** analysis. Appellants respectfully pointed out in the Response to the Final Action that **forensic** analysis is used to specifically identify individual members of the human population based simply on the presence or absence of one or more polymorphisms. Appellants reiterate that **forensic** analysis does not require **any information at all** about the ultimate biological function of the encoded protein, or require that the mutation cause a "disease or condition". Using the polymorphic marker as described in the specification as originally field, the skilled artisan can distinguish members of a population from one another without any additional research. In the worst case scenario, this polymorphic marker is useful to distinguish 50% of the population (in other words, the marker being present in half of the population). Appellants point out that the ability of a polymorphic marker to distinguish at least 50% of the population is an inherent feature of any polymorphic marker, and this feature is well understood by those of skill in the art. Appellants note that as a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988). Appellants respectfully point out that all that is required to support this assertion of utility is for the skilled artisan to believe that the presently described polymorphic marker could be useful in forensic analysis. The fact that forensic biologists use polymorphic markers such as that described by Appellants **every day** provides more than ample support for the assertion that forensic biologists would also be able to use the specific polymorphic marker described by Appellants in the same fashion. Therefore, the presently claimed sequence clearly has a substantial and well established utility. The ability to eliminate 50% of the population from a forensic analysis **clearly** is a real world, practical utility.

Furthermore, Appellants submit that the asserted forensic utility is specific precisely because it cannot be applied to just any polynucleotide. In fact, the basis for forensic analysis is the fact that such polymorphic markers are **not** present in all other nucleic acids, but in fact specific and unique to only a certain subset of the population. Additionally, until a polymorphic marker is actually described it cannot be used in forensic analysis. Put another way, simply because there is a likelihood, even a significant likelihood, that a particular nucleic acid sequence will contain a polymorphism and thus be useful in forensic analysis, until such a polymorphism is actually identified and described, such a likelihood is **meaningless**. Additionally, as set forth in the Response

to the First Action and the Response to the Final Action, the requirement for a **specific** utility, which is the proper standard for utility under 35 U.S.C. § 101, should not be confused with the requirement for a **unique** utility, which is clearly an improper standard. As clearly stated by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991; "*Carl Zeiss*"):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

In other words, just because other (possibly better) polymorphic markers from the human genome have been described, or that additional information about the presently described polymorphic markers can be gained through the use of these markers, does not establish that the presently described polymorphic markers lack a specific utility. Furthermore, the requirement for a unique utility is clearly not the standard adopted by the Patent and Trademark Office. If every invention were required to have a unique utility, the Patent and Trademark Office would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, such as cancer, just to name a few particular examples, because the utility of each of these compositions is applicable to the broad class in which each of these compositions falls: all batteries have the same utility, specifically to provide electrical power; all automobile tires have the same utility, specifically for use on automobiles; all golf balls and golf clubs have the same utility, specifically for use in the game of golf; and all cancer treatments have the same utility, specifically, to treat cancer. However, only the briefest perusal of virtually any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions nearly every week. Furthermore, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. In view of the above standards and "common sense" analysis, there can be little question that the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Furthermore, as the presently described polymorphism is a part of the family of polymorphisms that have a well established utility, the Federal Circuit's holding in *In re Brana,*

(34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*") is directly on point. In *Brana*, the Federal Circuit admonished the Patent and Trademark Office for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted, emphasis added. As set forth above, the present polymorphism is useful in forensic analysis as described in the specification as originally filed, without the need for any further research. As discussed above, even if the use of this polymorphic marker provided additional information on the percentage of particular subpopulations that contain this polymorphic marker, this would not mean that "additional research" is needed in order for this marker as it is presently described in the instant specification to be of use to forensic science. As stated above, using the polymorphic marker as described in the specification as originally field can definitely distinguish members of a population from one another. However, even if, *arguendo*, further research might be required in certain aspects of the present invention, this does not preclude a finding that the invention has utility, as set forth by the Federal Circuit's holding in *Brana*, which

clearly states, as highlighted in the quote above, that "pharmaceutical inventions, necessarily includes the expectation of further research and development" (*Brana* at 1442-1443, emphasis added). In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). Again, as a matter of law, it is well settled that a patent need not disclose what is well known in the art (*In re Wands, supra*).

Importantly, it has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974; "*Langer*"); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971). As set forth in *In re Langer* (183 USPQ 288 (CCPA 1974); "*Langer*"):

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Langer at 297, emphasis in original. As set forth in the MPEP, "Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art" (MPEP, Eighth Edition at 2100-40, emphasis added). Thus, absent such evidence from the Examiner concerning the use of the presently described polymorphism in forensic analysis, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Additionally, Appellants pointed out in both the Response to the First Action and the Response to the Final Action that Appellants' assertion in the specification as originally filed that the presently claimed sequence encodes a member of the platelet derived growth factor (PDGF) family (see the specification as originally filed, at least from page 2, line 34 to page 3, line 1) is supported by the fact that four sequences sharing 100% percent identity at the protein level over an

extended region of the claimed sequence are present in the leading scientific repository for biological sequence data (GenBank), and have been annotated by third party scientists who are *wholly unaffiliated with Appellants* as "Homo sapiens platelet derived growth factor C" (Li *et al.*, *Nat. Cell Biol.* **2**:302-309, 2000 and Gilbertson *et al.*, *J. Biol. Chem.* **276**:27406-27414, 2001; GenBank accession numbers NM_016205 and AF260738, respectively; copies of the abstracts, alignments and GenBank reports that were provided with the Response to the First Action and the Response to the Final Action are provided in **Exhibit A**), "Homo sapiens secretory growth factor-like protein fallotein" (which is a member of the PDGF family; Tsai *et al.*, *Biochim. Biophys. Acta* **1492**:196-202, 2000; copies of the abstract, alignment and GenBank report that were provided with the Response to the First Action and the Response to the Final Action are provided in **Exhibit B**), and "Homo sapiens hSCDGF mRNA for spinal-cord-derived growth factor (which is also a member of the PDGF family; Hamada *et al.*, *FEBS Lett.* **475**:97-102, 2000; copies of the abstract, alignment and GenBank report that were provided with the Response to the First Action and the Response to the Final Action are provided in **Exhibit C**). Appellants respectfully pointed out that the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. Given all of these GenBank annotations and scientific manuscripts, there can be no question that those skilled in the art would clearly believe that Appellants' sequence is a member of the platelet derived growth factor family. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

In the Final Action, the Examiner questioned this assertion of utility, stating that "the polypeptide taught by the specification will not have activity as taught by Li *et al.*" (The Final Action bridging pages 4 and 5). Appellants pointed out in the Response to the Final Action that this argument is not particularly germane to Appellants' assertion, since the alignments in **Exhibits A, B** and **C**, above, were provided to illustrate the extensive homology between the presently claimed sequence and a variety of members of the platelet derived growth factor family, not to show identity to any one specific members of the platelet derived growth factor family. Thus, while Appellants have provided evidence of record that conclusively establishes that those skilled in the art would believe that the specifically claimed sequence encodes a member of the platelet derived growth factor family, the Examiner has provided no evidence that directly establishes that the specifically claimed

sequence does not encode a member of the platelet derived growth factor family. Accordingly, the evidence of record compels a finding that the present invention has a patentable utility.

In the First Action, the Examiner cited an article by Skolnick *et al.* (*Trends in Biotech.* **18**:34-39, 2000; "Skolnick"), an issued U.S. Patent to Tischer *et al.* (U.S. Patent No. 5,194,596; "Tischer"), and an article by Yan *et al.* (*Science* **290**:523-527, 2000; "Yan") to support the alleged lack of utility based upon protein homology such as that shown by Appellants above. Skolnick is cited for the proposition that "(k)nowing the protein structure by itself is insufficient to annotate a number of functional classes and is also insufficient for annotating the specific details of protein function" (the First Action at page 4, quoting Skolnick at page 36; emphasis added). However, Skolnick concerns predicting protein function not by overall amino acid homology to other family members, but instead concerns prediction of function based on the presence of certain functional "motifs" present within a given protein sequence. Thus, Skolnick does not apply to the current situation, where overall protein homology is used to assign function to a particular sequence. However, even in the event that Skolnick is applicable, Skolnick itself concludes that "sequence-based approaches to protein-function prediction have proved to be very useful" (Skolnick at page 37), admitting that such methods have correctly assigned function in 50-70% of the cases. Thus, Skolnick does not support the Examiner's allegation that the presently claimed sequence lacks a patentable utility.

Tischer is cited for the proposition that individual members of a protein family can "have distinct, and sometimes even opposite, biological activities" (the First Action at page 4). While this may in fact be the case, an unusual case such as this, particularly one disclosed in a patent based on an application filed in 1989, ten years before the filing of the present application, hardly represents the view of those skilled in the art at the time of the present application regarding prediction of protein function based on homology. Appellants submit that, as described above, those skilled in the art in 1999 would clearly believe that Appellants' sequence is a platelet derived growth factor.

Regarding Yan, only one example is cited in Yan, specifically, two isoforms of the anhidrotic ectodermal dysplasia (EDA) gene, where a two amino acid change conforms one isoform (EDA-A1) into the second isoform (EDA-A2). However, while it is true that this amino acid change results in binding to different receptors, it is important to note that the different receptors bound by the two isoforms are in fact related (Yan at page 523). Furthermore, the EDA-A2 receptor was correctly

identified as a member of the tumor necrosis factor receptor superfamily based solely on sequence similarity (Yan at page 523). Thus, Yan does not suggest a high level of uncertainty in assigning function based on sequence, and thus also does not support the alleged lack of utility.

Furthermore, with regard to the citation of journal articles to support an allegation of a lack of utility, the PTO has repeatedly attempted to deny the utility of nucleic acid sequences based on a small number of publications that call into doubt prediction of protein function from homology information and the usefulness of bioinformatic predictions, of which these articles are merely the latest examples. Appellants readily agree that there is not 100% consensus within the scientific community regarding prediction of protein function from homology information, and further agree that prediction of protein function from homology information is not 100% accurate. However, Appellants respectfully point out that the lack of 100% consensus on prediction of protein function from homology information is **completely irrelevant** to the question of whether the claimed nucleic acid sequence has a substantial and specific utility, and that 100% accuracy of prediction of protein function from homology information is **not the standard** for patentability under 35 U.S.C. § 101. Appellants respectfully point out that, as discussed above, the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be **believable**. Appellants submit that the overwhelming majority of those of skill in the relevant art would **believe** prediction of protein function from homology information and the usefulness of bioinformatic predictions to be powerful and useful tools, as evidenced by hundreds if not thousands of journal articles (which Appellants will submit to the Office if the Board truly doubts Appellants' assertion that the overwhelming majority of those of skill in the art place a high value on prediction of protein function from homology information and the usefulness of bioinformatic predictions), and would thus **believe** that Appellants sequence is a member of the platelet derived growth factor family. As **believability** is the standard for meeting the utility requirement of 35 U.S.C. § 101, and **not** 100% consensus or 100% accuracy, Appellants submit that the present claims must clearly meet the requirements of 35 U.S.C. § 101.

Furthermore, the **PTO itself** does not require 100% identity between proteins to establish functional homology. Example 10 of the PTO's Revised Interim Utility Guidelines Training Materials only requires a similarity score greater than 95% to establish functional homology. Thus,

scientific publications that generally assert that very small changes between amino acid sequences can lead to changes in function, or publications describing specific examples of proteins, distinct from Appellants sequence, where a minor change in amino acid sequence has lead to a change in function, have been viewed by the **PTO itself** as irrelevant to the question of utility, and thus do not support the Examiner's allegation that the presently claimed sequence lacks utility. Therefore, the present utility rejection must fail as a matter of policy, as a matter of science, and as a matter of law.

In the Advisory Action, the Examiner continues to question Appellants' assertion of utility, stating "that the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product, if the claimed DNA had a specific and substantial utility such as it hybridizes near a disease-associated gene or it has gene regulating activity" (the Advisory Action at page 2). Appellants respectfully point out that evidence showing that the presently claimed sequence is a "disease-associated gene" or "has gene regulating activity" is **not** the standard for patentability under 35 U.S.C. § 101 (*In re Brana, supra*). Thus, this argument also does not support the Examiner's allegation that the presently claimed sequence lacks a patentable utility.

Therefore, Appellants pointed out in the Response to the First Action and the Response to the Final Action that given the well established biological and medical relevance of platelet derived growth factor proteins, those of skill in the art would readily appreciate the importance of tracking the expression of the genes encoding the described proteins, as described at least at page 5, lines 4-7, in priority document 60/162,547, which was incorporated in its entirety by reference into the present specification as originally filed. In particular, the specification describes how the described sequences can be represented using a gene chip format to provide a high throughput analysis of the level of gene expression. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776 (**Exhibits D-I**; copies of issued U.S. Patents not provided pursuant to current United States Patent and Trademark Office policy). Given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. As the present sequences are specific markers of the human genome (see below), and such specific markers are targets for the discovery of drugs that are associated with human disease,

those of skill in the art would instantly recognize that the present nucleotide sequences would be ideal, novel candidates for assessing gene expression using such DNA chips. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Further evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies that have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company (Rosetta Inpharmatics) was viewed to have such "real world" value that it was acquired by large a pharmaceutical company (Merck) for significant sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, there can be no doubt that the skilled artisan would know how to use the presently claimed sequences (see Section VIII(B), below), strongly arguing that the claimed sequences have utility. Persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, *Science* **291**:1304, 2001). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, *Science* **291**:1153, 2001). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years). Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Advisory Action questions this assertion of utility, stating that "(c)ontrary to Applicants' assertion, the claims in the cited patents are drawn to the apparatus, the instant claims are drawn to a (*sic*) isolated nucleic acid" (the Advisory Action at page 2). Appellants state for the record that

it has **never** been asserted by Appellants that the present claims are "drawn to" gene chips. Rather, it is, and always has been, Appellants position that the presently claimed sequences have utility in assessing gene expression patterns **using** such gene chips as those described in the issued U.S. Patents described above. Thus, this argument in no way supports the alleged lack of utility. Additionally, Appellants reiterate that the requirements of a **specific** utility should not be confused with a requirement for a **unique** utility. Simply because other polynucleotide sequences can be used to track gene expression on a gene chip does not mean that the use of the presently claimed nucleic acid sequence in gene chip applications is not a specific utility (*Carl Zeiss, supra*).

Although Appellants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), Appellants noted in the Response to the First Action and the Response to the Final Action, as a further example of the utility of the presently claimed polynucleotide, as described in the specification at least at page 10, lines 34-35, the present nucleotide sequences have a specific utility in "determining the genomic structure", for example in the identification of coding sequence and mapping the gene to a particular chromosome. This is evidenced by the fact that SEQ ID NO:6 can be used to map the 5 coding exons on chromosome 4 (present within two overlapping chromosome 4 clones; GenBank Accession Numbers AC093325 and AC092608; copies of the alignments and the first page from the GenBank reports that were provided with the Response to the First Action and the Response to the Final Action are provided in **Exhibit J**). Appellants respectfully remind the Board that only a minor percentage (2-4%) of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). Such biologically validated splice junctions are superior to splice junctions that may have been predicted from genomic sequence alone, and, as detailed in the specification, at least

from page 10, line 36 to page 11, line 3, that "sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), *etc.*, that can be used in diagnostics and pharmacogenomics". Appellants respectfully submit that the practical scientific value of biologically validated, expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts.

Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of human chromosome 4 that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence. For further evidence in support of the Appellants' position, the Board is requested to review, for example, section 3 of Venter *et al.* (*supra*, at pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Examiner also questioned these asserted utilities, stating that "any chromosome region 4 gene can be used to map that particular area of the chromosome" (the Final Action at page 6), and reiterating this position in the Advisory Action: "there are other sequence (*sic*) which (*sic*) would map to the same region" (the Advisory Action at page 2). First, Appellants respectfully point out that only those small percentage of nucleotide sequences that are located in this region of chromosome 4 can be used in such a manner, and not just "any polynucleotide". Second The Examiner once again seems to be confusing the requirements of a **specific** utility with a **unique** utility. The fact that a small number of other nucleotide sequences could be used to map the protein

coding regions in this specific region of chromosome 4 does not mean that the use of Appellants' sequence to map the protein coding regions of chromosome 4 is not a specific utility (*Carl Zeiss, supra*). The holding in *Carl Zeiss*, and particularly the quote provided above, clearly states that an invention does not need to be the only way to accomplish a certain result. Thus, the question of whether or not other nucleic acid sequences can be used to assess gene expression using DNA chips is completely irrelevant to the present utility inquiry. The only relevant question in regard to meeting the standards of 35 U.S.C. § 101 is whether **every** nucleic acid can be so used - and the clear answer to this question is an emphatic **no**. Importantly, the holding in *Carl Zeiss* is **mandatory legal authority** that essentially controls the outcome of the present case. This case, and particularly the cited quote, **directly** rebuts the Examiner's argument. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Furthermore, regarding the utility requirements under 35 U.S.C. § 101, the Federal Circuit has clearly stated "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 185 F.3d 1364, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable *(State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 149 F.3d 1368, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (U.S., 1980)). Thus, based on the relevant case law, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Finally, While Appellants are well aware of the new Utility Guidelines set forth by the USPTO, Appellants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or

particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Appellants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Board is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (**Exhibits K-M**; each of which claims short polynucleotides; copies of issued U.S. Patents not provided pursuant to current United States Patent and Trademark Office policy), and recently issued U.S. Patent No. 6,340,583 (**Exhibit N**; which includes no working examples; copy of issued U.S. Patent not provided pursuant to current United States Patent and Trademark Office policy), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section VIII(B), below), Appellants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Appellants understand that each application is examined on its own merits, Appellants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Thus, holding Appellants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

For each of the foregoing reasons, Appellants submit that the rejection of claims 4-11 under 35 U.S.C. § 101 must be overruled.

B. Are Claims 4-11 Unusable Due to a Lack of Patentable Utility?

The Final Action next rejects claims 4-11 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by either a clear asserted utility or a well-established utility.

The arguments detailed above in Section VIII(A) concerning the utility of the presently claimed sequences are incorporated herein by reference. As the Federal Circuit and its predecessor have determined that the utility requirement of Section 101 and the how to use requirement of Section 112, first paragraph, have the same basis, specifically the disclosure of a credible utility (*In re Brana, supra*; *In re Jolles*, 628 F.2d 1322, 1326 n.11, 206 USPQ 885, 889 n.11 (CCPA 1980); *In re Fouche*, 439 F.2d 1237, 1243, 169 USPQ 429, 434 (CCPA 1971)), Appellants submit that as claims 4-11 have been shown to have "a specific, substantial, and credible utility", as detailed in Section VIII(A) above, the present rejection of claims 4-11 under 35 U.S.C. § 112, first paragraph, cannot stand.

Appellants therefore submit that the rejection of claims 4-11 under 35 U.S.C. § 112, first paragraph, must be overruled.

C. Are Claims 4, 7 and 8 Enabled?

The Final Action next rejected claims 4, 7 and 8 under 35 U.S.C. § 112, first paragraph, as allegedly not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

Appellants have repeatedly pointed out that there is absolutely no requirement that all species of an invention must have all of the exact same properties. While the Examiner apparently agrees, stating "(t)here is no requirement that all species of an invention have the exact same properties" (the Final Action at page 8), **every single argument** put forth by the Examiner to support the present rejection hinges on the fact that fragments of SEQ ID NO:6 do not have the same functional characteristics as the full length sequence of SEQ ID NO:6, or the full length amino acid sequence of SEQ ID NO:7. In the First Action, the Examiner stated that "the specification is not enabled for fragments of polynucleotides" because "the changes which can be made in the structure and still maintain sufficient activity is unpredictable" (the First Action at page 6). The Examiner appears to be requiring the polynucleotide fragments to have the same "structure" and "activity" as the full length protein encoded by SEQ ID NO:6. In the Final Action, the Examiner states that "there is no assurance that when the DNA is expressed, the protein would have the desirable properties of the invention" (the Final Action bridging pages 8 and 9). The Examiner appears to believe that the only

"desirable property" that a polynucleotide fragment of the present invention could have is the specific biological properties of the full length protein encoded by SEQ ID NO:6. In the Advisory Action, the Examiner continues this misguided analysis of the enablement requirement: "(a) fragment containing at least 24 contiguous bases could not be used in recombinant expression because a functional protein would not be made" (the Advisory Action at page 2). **None** of these arguments are in the least bit consistent with the Examiner's repeated assertions that "(t)he Examiner stated specifically that there is no requirement that all species of an invention have the exact same properties" (the Advisory Action at page 2), and, most importantly, in **no way whatsoever** support the allegation that claims 4, 7 and 8 are not enabled.

The Examiner stated that "the rejected claims encompass fragments of NHP which (sic) do not have a property" (Action at page 8), and reiterates this position in the Advisory Action. However, as pointed out by Appellants in the Response to the Final Action, this allegation is quite simply **completely and totally false**. **At the very least**, as there are no art rejections against polynucleotide fragments comprising at least 24 contiguous bases of nucleotide sequence from SEQ ID NO:6, these fragments have the property of being unique identifiers of SEQ ID NO:6. Appellants also pointed out that significant commercial exploitation of nucleic acid sequences requires no more information than the nucleic acid sequence itself. Applications ranging from gene expression analysis or profiling (utilizing, for example, arrays of short, overlapping or non-overlapping, oligonucleotides and DNA chips, as described in Section VIII(A), above) to chromosomal mapping (utilizing, for example, short oligonucleotide probes or full length DNA sequences, as described in Section VIII(A), above) are practiced utilizing nucleic acid sequences and techniques that are well-known to those of skill in the art. The widespread commercial exploitation of nucleic acid sequence information points to the level of skill in the art, and the enablement provided by disclosures such as the present specification, which include specific nucleic acid sequences and guidance regarding the various uses of such sequences. Appellants pointed out in both the Response to the First Action and the Response to the Final Action that it is well established that the enablement requirement is met if any use of the invention (or in this case, certain species of the invention) is provided (*In re Nelson*, 126 USPQ 242 (CCPA 1960); *Cross v. Iizuka, supra*). "The enablement requirement is met if the description enables any mode of making and using the invention." *Johns Hopkins Univ. v.*

CellPro, Inc., 47 USPQ2d 1705, 1719 (Fed. Cir. 1998), citing *Engel Indus., Inc. v. Lockformer Co.*, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991). The skilled artisan can clearly make and use the claimed polynucleotides, which is **all that is required** to meet the enablement requirement under 35 U.S.C. § 112, first paragraph. As this is the proper standard, and **not** that the polynucleotide fragments "maintain sufficient activity" or encode "a functional protein", claims 4, 7 and 8 clearly meet the requirements of 35 U.S.C. § 112, first paragraph.

The Examiner then states that "(i)n the absence of specific hybridization language, the polynucleotide fragment may correspond to any region that is highly conserved in a gene family" and that "(i)t allows imperfect matches and carry (*sic*) the risk of obtaining false signals from unrelated DNA sequences", and therefore "(t)he specification is not enabled for unrelated sequences which (*sic*) may cross hybridize with the instant invention" (the Advisory Action at page 2). Appellants respectfully point out that claims 4, 7 and 8 do **not** concern hybridization **at all**. Claim 4 (and therefore dependent claims 7 and 8) requires "at least 24 contiguous bases of nucleotide sequence first disclosed in the NHP gene described in SEQ ID NO:6", and thus does not allow "imperfect matches". Furthermore, as there are **no** art rejections against polynucleotide fragments comprising at least 24 contiguous bases of nucleotide sequence from SEQ ID NO:6, the Examiner's conclusion that "the polynucleotide fragment may correspond to any region that is highly conserved in a gene family" is completely and totally unfounded. Thus, these arguments in **no way** support the Examiner's position that claims 4, 7 and 8 are not enabled.

The Examiner questions the teaching and guidance in the specification for certain aspects of the present invention. However, as discussed above, this requirement is completely misplaced. There is sufficient knowledge and technical skill in the art for a skilled artisan to be able to make and use the claimed DNA species in a number of different aspects of the invention entirely without further details in a patent specification. For example, it is not unreasonable to expect a Ph.D. level molecular biologist to be able to use the disclosed sequence to design oligonucleotide probes and primers and use them in, for example, PCR based screening and detection methods to obtain the described sequences and/or determine tissue expression patterns. Nevertheless, the present specification provides highly detailed descriptions of techniques that can be used to accomplish many different aspects of the claimed invention, including recombinant expression, site-specific

mutagenesis, *in situ* hybridization, and large scale nucleic acid screening techniques, and properly incorporates by reference a montage of standard texts into the specification, such as Sambrook *et al.* (*Molecular Cloning, A Laboratory Manual*) and Ausubel *et al.* (*Current Protocols in Molecular Biology*) to provide even further guidance to the skilled artisan. Incorporation of material into the specification by reference is proper. *Ex parte Schwarze*, 151 USPQ 426 (PTO Bd. App. 1966). The § 112, first paragraph rejection is thus *prima facie* improper:

> As a matter of patent office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971), emphasis as in original. In any event, an alleged lack of express teaching is insufficient to support a first paragraph rejection where one of skill in the art would know how to perform techniques required to perform at least one aspect of the invention. As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands, supra*. In fact, it is preferable that what is well known in the art be omitted from the disclosure. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986). As standard molecular biological techniques are routine in the art, such protocols do not need to described in detail in the specification.

The Examiner has repeatedly stated that the specification provides insufficient guidance regarding the biological function or activity of certain of the claimed compositions. However, such an enablement standard conflicts with established patent law. As discussed *In re Brana* (*supra*; "*Brana*"), the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Examiner cited *In re Wands* (*supra*; "*Wands*") for the proposition that the present invention could not be practiced without "undue experimentation". However, it is important to remember that in assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin, supra*. In *Wands*, the P.T.O. took the position that the applicant failed to demonstrate that the disclosed biological processes of

immunization and antibody selection could reproducibly result in a useful biological product (antibodies from hybridomas) within the scope of the claims. In its decision overturning the P.T.O.'s rejection, the Federal Circuit found that Wands' demonstration of success in four out of nine cell lines screened was sufficient to support a conclusion of enablement. The court emphasized that the need for some experimentation requiring, *e.g.*, production of the biological material followed by routine screening, was not a basis for a finding of non-enablement, stating:

> Disclosure in application for the immunoassay method patent does not fail to meet enablement requirement of 35 USC 112 by requiring 'undue experimentation,' even though production of monoclonal antibodies necessary to practice invention first requires production and screening of numerous antibody producing cells or 'hybridomas,' since practitioners of art are prepared to screen negative hybridomas in order to find those that produce desired antibodies, since in monoclonal antibody art one 'experiment' is not simply screening of one hybridoma but rather is entire attempt to make desired antibody, and since record indicates that amount of effort needed to obtain desired antibodies is not excessive, in view of Applicants' success in each attempt to produce antibody that satisfied all claim limitations.

Wands at 1400. Thus, the need for some experimentation does not render the claimed invention unpatentable under 35 U.S.C. § 112, first paragraph. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., supra.*

Furthermore, a specification "need describe the invention only in such detail as to enable a person skilled in the most relevant art to make and use it." *In re Naquin*, 158 USPQ 317, 319 (CCPA 1968); emphasis added. The present claims are thus enabled as they are supported by a specification that provides sufficient description to enable the skilled person to make and use the invention as claimed. Appellants stress that enablement must be analyzed, not in a vacuum, but "as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." *In re Moore*, 169 USPQ 236, 238 (CCPA 1971). As described in detail above, the specification details numerous applications in which claimed nucleotide sequences can be used, for example, to track gene expression using gene chips. Further, since public domain nucleotide sequences that have not been associated with any particular biological function, let alone validated as coding sequences, are used every day in gene chip applications, it defies logic that undue experimentation would be required to use the presently described nucleotide sequences, which have been biologically validated as coding

sequences, in the very same gene chip applications. Therefore, claims 4, 7 and 8 clearly meet the requirements of 35 U.S.C. § 112, first paragraph.

Appellants therefore submit that the rejection of claims 4, 7 and 8 under 35 U.S.C. § 112, first paragraph, must be overruled.

D. Does Claim 4 Lack Sufficient Written Description?

The Final Action next rejected claim 4 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

35 U.S.C. § 112, first paragraph, requires that the specification contain a written description of the invention. The Federal Circuit in *Vas-Cath Inc. v. Mahurkar* (19 USPQ2d 1111 (Fed. Cir. 1991); "*Vas-Cath*") held that an "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*." *Vas-Cath*, at 1117, emphasis in original. However, it is important to note that the above finding uses the terms reasonable clarity to those skilled in the art. Further, the Federal Circuit in *In re Gosteli* (10 USPQ2d 1614 (Fed. Cir. 1989); "*Gosteli*") held:

> Although [the applicant] does not have to describe exactly the subject matter claimed, . . . the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.

Gosteli at 1618, emphasis added. Additionally, *Utter v. Hiraga* (6 USPQ2d 1709 (Fed. Cir. 1988); "*Utter*"), held "(a) specification may, within the meaning of 35 U.S.C. § 112 ¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses" (*Utter*, at 1714). Therefore, all Appellants must do to comply with 35 U.S.C. § 112, first paragraph, is to convey the invention with reasonable clarity to the skilled artisan.

The Examiner stated that claim 4 fails to meet the written description requirement because the specification "discloses only a structural feature" (the Final Action at page 10), and reiterates this position in the Advisory Action. Appellants have repeatedly pointed out that this is **all that is required** for claim 4 to meet the written description requirement of 35 U.S.C. § 112, first paragraph.

The Federal Circuit has held that an adequate description of a chemical genus "requires a precise definition, such as by structure, formula, chemical name or physical properties" sufficient to distinguish the genus from other materials. *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993; "*Fiers*"). *Fiers* goes on to hold that the "application satisfies the written description requirement since it sets forth the . . . nucleotide sequence" (*Fiers* at 1607). In other words, provision of a structure and formula - the nucleotide sequence - renders the application in compliance with 35 U.S.C. § 112, first paragraph.

More recently, the standard for complying with the written description requirement in claims involving chemical materials has been explicitly set forth by the Federal Circuit:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. *Regents of Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Thus, a claim describing a genus of nucleic acids by structure, formula, chemical name or physical properties sufficient to allow one of ordinary skill in the art to distinguish the genus from other materials meets the written description requirement of 35 U.S.C. § 112, first paragraph. As further elaborated by the Federal Circuit in *Regents of Univ. of California v. Eli Lilly and Co.*:

> In claims to genetic material ... a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA', without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art cannot, as one can do with a fully described genus, visualize or recognize the identity of members of the genus. (Emphasis added)

Thus, as opposed to the situation set forth in *Regents of Univ. of California v. Eli Lilly and Co.* and *Fiers*, the nucleic acid sequences of the present invention are not distinguished on the basis of function, or a method of isolation, but in fact are distinguished by structural features - a chemical formula, *i.e.*, the *sequence itself.*

Using the nucleic acid sequences of the present invention (as set forth in the Sequence Listing), the skilled artisan would readily be able to **distinguish** the claimed nucleic acids from other

materials on the basis of the specific **structural** description provided. Polynucleotides comprising at least 24 contiguous bases from SEQ ID NO:6 are within the genus of the instant claims, while those that lack this structural feature lie outside the genus. The claimed genus of polynucleotides is clearly defined in structural terms, which is **all that is required** of claim 4 in order to meet the written description requirement of 35 U.S.C. § 112, first paragraph.

The Examiner states that "(t)hese 24 contiguous bases can come from a completely different nucleotide sequence, not just SEQ ID NO:6" (the Advisory Action at page 2). Appellants reiterate that, as there are **no** art rejections against polynucleotide fragments comprising at least 24 contiguous bases of nucleotide sequence from SEQ ID NO:6, this unsubstantiated conclusion by the Examiner in **no way** satisfies the Examiner's burden of establishing a prima facie case that claim 4 lacks sufficient written description support, let alone serves to overcome the controlling legal precedent cited by Appellants. As the claimed genus of polynucleotides is clearly defined in **structural** terms that allows the skilled artisan to **distinguish** the claimed nucleic acids from other materials, claim 4 clearly meets the written description requirement of 35 U.S.C. § 112, first paragraph.

For each of the foregoing reasons, Appellants submit that the rejection of claim 4 under 35 U.S.C. § 112, first paragraph, must be overruled.

IX. APPENDIX

The claims involved in this appeal are as follows:

4. (Original) An isolated nucleic acid molecule comprising at least 24 contiguous bases of nucleotide sequence first disclosed in the NHP gene described in SEQ ID NO:6.

5. (Previously Presented) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO:7; and

(b) hybridizes to the nucleotide sequence of SEQ ID NO:6 or the complement thereof under highly stringent conditions of 0.5 M $NaHPO_4$, 7% sodium dodecyl sulfate (SDS) and 1 mM EDTA at 65°C and washing in 0.1x SSC/0.1%SDS at 68°C.

6. (Original) An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:7.

7. (Previously Presented) A recombinant expression vector comprising the isolated nucleic acid molecule of claim 4.

8. (Previously Presented) A host cell comprising the recombinant expression vector of claim 7.

9. (Previously Presented) The isolated nucleic acid molecule of claim 4, comprising the nucleic acid sequence of SEQ ID NO:6.

10. (Previously Presented) The recombinant expression vector of claim 7, wherein said nucleic acid molecule encodes the amino acid sequence shown in SEQ ID NO:7.

11. (Previously Presented) The recombinant expression vector of claim 10, wherein said

nucleic acid molecule comprises the nucleic acid sequence of SEQ ID NO:6.

X. CONCLUSION

Appellants respectfully submit that, in light of the foregoing arguments, the Final Action's conclusion that claims 4-11 lack a patentable utility and are unusable by the skilled artisan due to a lack of patentable utility, that claims 4, 7 and 8 are not enabled, and that claim 4 lacks sufficient written description, is unwarranted. It is therefore requested that the Board overturn the Final Action's rejections.

Respectfully submitted,

February 19, 2004
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Li X, Ponten A, Aase K, Karlsson L, Abramsson A, Uutela M, Backstrom G, Hellstrom M, Bostrom H, Li H, Soriano P, Betsholtz C, Heldin CH, Alitalo K, Ostman A, Eriksson U.

Ludwig Institute for Cancer Research, Stockholm, Sweden.

Platelet-derived growth factors (PDGFs) are important in many types of mesenchymal cell. Here we identify a new PDGF, PDGF-C, which binds to and activates the PDGF alpha-receptor. PDGF-C is activated by proteolysis and induces proliferation of fibroblasts when overexpressed in transgenic mice. In situ hybridization analysis in the murine embryonic kidney shows preferential expression of PDGF-C messenger RNA in the metanephric mesenchyme during epithelial conversion. Analysis of kidneys lacking the PDGF alpha-receptor shows selective loss of mesenchymal cells adjacent to sites of expression of PDGF-C mRNA; this is not found in kidneys from animals lacking PDGF-A or both PDGF-A and PDGF-B, indicating that PDGF-C may have a unique function.

PMID: 10806482 [PubMed - indexed for MEDLINE]

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1: J Biol Chem 2001 Jul 20;276(29):27406-14

Platelet-derived growth factor C (PDGF-C), a novel growth factor that binds to PDGF alpha and beta receptor.

Gilbertson DG, Duff ME, West JW, Kelly JD, Sheppard PO, Hofstrand PD, Gao Z, Shoemaker K, Bukowski TR, Moore M, Feldhaus AL, Humes JM, Palmer TE, Hart CE.

ZymoGenetics Inc., Seattle, Washington 98102, USA. gilbertd@zgi.com

We have characterized platelet-derived growth factor (PDGF) C, a novel growth factor belonging to the PDGF family. PDGF-C is a multidomain protein with the N-terminal region homologous to the extracellular CUB domain of neuropilin-1, and the C-terminal region consists of a growth factor domain (GFD) with homology to vascular endothelial growth factor (25%) and PDGF A-chain (23%). A serum-sensitive cleavage site between the two domains allows release of the GFD from the CUB domain. Competition binding and immunoprecipitation studies on cells bearing both PDGF alpha and beta receptors reveal a high affinity binding of recombinant GFD (PDGF-CC) to PDGF receptor-alpha homodimers and PDGF receptor-alpha/beta heterodimers. PDGF-CC exhibits greater mitogenic potency than PDGF-AA and comparable or greater mitogenic activity than PDGF-AB and PDGF-BB on several mesenchymal cell types. Analysis of PDGF-CC in vivo in a diabetic mouse model of delayed wound healing showed that PDGF-CC significantly enhanced repair of a full-thickness skin excision. Together, these studies describe a third member of the PDGF family (PDGF-C) as a potent mitogen for cells of mesenchymal origin in in vitro and in vivo systems with a binding pattern similar to PDGF-AB.

PMID: 11297552 [PubMed - indexed for MEDLINE]

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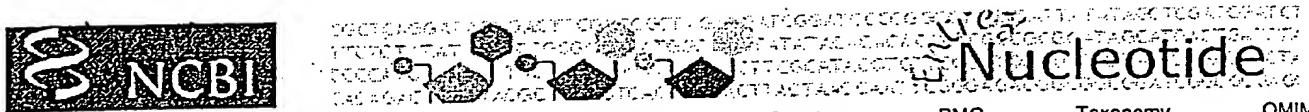

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Links

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            Betsholtz,C., Heldin,C.H., Alitalo,K., Ostman,A. and Eriksson,U.
  TITLE     PDGF-C is a new protease-activated ligand for the PDGF
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  JOURNAL   Nat. Cell Biol. 2 (5), 302-309 (2000)
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   PUBMED   10806482
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  AUTHORS   Hamada,T., Ui-Tei,K. and Miyata,Y.
  TITLE     A novel gene derived from developing spinal cords, SCDGF, is a
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  JOURNAL   FEBS Lett. 475 (2), 97-102 (2000)
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  TITLE     Identification of a novel platelet-derived growth factor-like gene,
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  JOURNAL   Biochim. Biophys. Acta 1492 (1), 196-202 (2000)
  MEDLINE   20461776
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  AUTHORS   Zwerner,J.P. and May,W.A.
  TITLE     PDGF-C is an EWS/FLI induced transforming growth factor in Ewing
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  JOURNAL   Oncogene 20 (5), 626-633 (2001)
  MEDLINE   21214457
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  AUTHORS   Uutela,M., Lauren,J., Bergsten,E., Li,X., Horelli-Kuitunen,N.,
            Eriksson,U. and Alitalo,K.
  TITLE     Chromosomal location, exon structure, and vascular expression
            patterns of the human PDGFC and PDGFC genes
  JOURNAL   Circulation 103 (18), 2242-2247 (2001)
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AUTHORS Gilbertson,D.G., Duff,M.E., West,J.W., Kelly,J.D., Sheppard,P.O., Hofstrand,P.D., Gao,Z., Shoemaker,K., Bukowski,T.R., Moore,M., Feldhaus,A.L., Humes,J.M., Palmer,T.E. and Hart,C.E.
TITLE Platelet-derived growth factor C (PDGF-C), a novel growth factor that binds to PDGF alpha and beta receptor
JOURNAL J. Biol. Chem. 276 (29), 27406-27414 (2001)
MEDLINE 21347863
PUBMED 11297552
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Summary: The protein encoded by this gene is a member of the platelet-derived growth factor family. The four members of this family are mitogenic factors for cells of mesenchymal origin and are characterized by a core motif of eight cysteines. This gene product appears to form only homodimers. It differs from the platelet-derived growth factor alpha and beta polypeptides in having an unusual N-terminal domain, the CUB domain.
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Revised: July 5, 2002.

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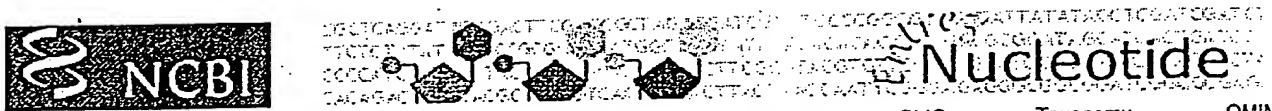

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  TITLE     Platelet-derived growth factor C (PDGF-C), a novel growth factor
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  JOURNAL   J. Biol. Chem. 276 (29), 27406-27414 (2001)
  MEDLINE   21347863
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  AUTHORS   Gao,Z., Hart,C., Piddington,C., Sheppard,P., Shoemaker,K.,
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  TITLE     Direct Submission
  JOURNAL   Submitted (26-APR-2000) Biomolecular Informatics, ZymoGenetics,
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Revised: July 5, 2002.

Mar 3 2003 10:13:39

1: Biochim Biophys Acta 2000 Jun 21;1492(1):196-202 Related Articles, Link

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Identification of a novel platelet-derived growth factor-like gene, fallotein, in the human reproductive tract.

Tsai YJ, Lee RK, Lin SP, Chen YH.

Division of Reproduction and Endocrinolgy, Department of Medical Research, Mackay Memorial Hospital, Tamshui, Taiwan.
yjtsai@ms1.mmh.org.tw

We isolated the cDNA of a novel platelet-derived growth factor-like gene from human endometrium. The gene was named fallotein; it was 3007 bases in length, and encoded a protein of 345 amino acids. Antiserum against the fallotein protein can recognize a specific protein in the fallopian tube, with a molecular size in accordance with the anticipated size of fallotein. Fallotein mRNA is expressed in two molecular sizes, 3.8 and 2.9 kb, with the former being more abundant. High expression of the gene was found in the prostate, testis, and uterus. A weaker expression signal was found in the spleen, thymus, and small intestine, but expression of fallotein in the colon and peripheral blood leukocytes was negligible.

PMID: 11004490 [PubMed - indexed for MEDLINE]

>AF091434 ACCESSION:AF091434 NID: gi 6002592 gb AF091434.1 AF091434
Homo sapiens secretory growth factor-like protein
fallotein mRNA, complete cds
Length = 3007

Score = 486 bits (1237), Expect = e-135
Identities = 234/234 (100%), Positives = 234/234 (100%)
Frame = +3

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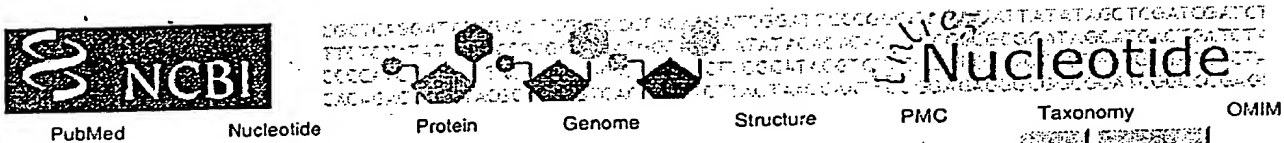

Links

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ACCESSION   AF091434
VERSION     AF091434.1  GI:6002592
KEYWORDS    .
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            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 3007)
  AUTHORS   Tsai,Y.J., Lee,R.K., Lin,S.P. and Chen,Y.H.
  TITLE     Identification of a novel platelet-derived growth factor-like gene,
            fallotein, in the human reproductive tract
  JOURNAL   Biochim. Biophys. Acta 1492 (1), 196-202 (2000)
  MEDLINE   20461776
   PUBMED   11004490
REFERENCE   2  (bases 1 to 3007)
  AUTHORS   Tsai,Y.J., Lee,R.K.K. and Lin,S.P.
  TITLE     Direct Submission
  JOURNAL   Submitted (14-SEP-1998) Dept. Medical Research, Mackay Memorial
            Hospital, 45 Min Sheng Road, Tamshui, Taipei County 25115, Taiwan
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Revised: July 5, 2002.

1: FEBS Lett 2000 Jun 16;475(2):97-102

Related Articles, Link

ELSEVIER SCIENCE FULL-TEXT ARTICLE

A novel gene derived from developing spinal cords, SCDGF, is a unique member of the PDGF/VEGF family.

Hamada T, Ui-Tei K, Miyata Y.

Department of Pharmacology, Nippon Medical School, Tokyo, Japan.

We isolated a novel gene designated spinal cord-derived growth factor (SCDGF). Its expression was increased in chick spinal cords with embryonic development and decreased after hatching. The amino acid sequences of chick and human SCDGFs revealed a putative signal sequence followed by a CUB domain and a region homologous to the members of the platelet-derived growth factor/vascular endothelial growth factor family. Furthermore, human SCDGF secreted from the cells showed a mitogenic activity for 10T1/2 cells in vitro. These results led us to speculate that SCDGF plays an important role in the development of the spinal cord.

PMID: 10858496 [PubMed - indexed for MEDLINE]

>AB033831 ACCESSION:AB033831 NID: gi 9392293 dbj AB033831.1 Homo sapiens hSCDGF mRNA for spinal cord-derived growth factor, complete cds
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Score = 486 bits (1237), Expect = e-135
Identities = 234/234 (100%), Positives = 234/234 (100%)
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☐ 1: AB033831. Homo sapiens hSCD...[gi:9392293]

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DEFINITION  Homo sapiens hSCDGF mRNA for spinal cord-derived growth factor,
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ACCESSION   AB033831
VERSION     AB033831.1  GI:9392293
KEYWORDS    spinal cord-derived growth factor; scdgf gene.
SOURCE      Homo sapiens (human)
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            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (sites)
  AUTHORS   Hamada,T., Ui-Tei,K. and Miyata,Y.
  TITLE     A novel gene derived from developing spinal cords, SCDGF, is a
            unique member of the PDGF/VEGF family
  JOURNAL   FEBS Lett. 475 (2), 97-102 (2000)
  MEDLINE   20317014
   PUBMED   10858496
REFERENCE   2  (bases 1 to 1817)
  AUTHORS   Hamada,T., Ui-Tei,K. and Miyata,Y.
  TITLE     Direct Submission
  JOURNAL   Submitted (25-OCT-1999) Tsuyoshi Hamada, Nippon Medical School,
            Department of Pharmacology; 1-1-5, Sendagi, Bunkyo-ku, Tokyo
            113-8602, Japan (E-mail:t-hamada@nms.ac.jp,
            Tel:81-3-3822-2131(ex.5277), Fax:81-3-5814-1684)
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Revised: July 5, 2002.

Mar 3 2003 10:13:39

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              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 77033 gagagatggcagttggacttagaagatctatataggccaacttggcaacttcttggcaag 76974
```

```
Query: 676   gcttttgttttggaagaaaatccagagg 704
             ||||||||||||||||||||||||||||
Sbjct: 76973 gcttttgttttggaagaaaatccagagg 76945


 Score =  396 bits (200), Expect = e-108
 Identities = 200/200 (100%)
 Strand = Plus / Minus

Query: 118    ggagtacaagatcctcagcatgagagaattattactgtgtctactaatggaagtattcac 177
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 154677 ggagtacaagatcctcagcatgagagaattattactgtgtctactaatggaagtattcac 154618

Query: 178    agcccaaggtttcctcatacttatccaagaaatacggtcttggtatggagattagtagca 237
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 154617 agcccaaggtttcctcatacttatccaagaaatacggtcttggtatggagattagtagca 154558

Query: 238    gtagaggaaaatgtatggatacaacttacgtttgatgaaagatttgggcttgaagaccca 297
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 154557 gtagaggaaaatgtatggatacaacttacgtttgatgaaagatttgggcttgaagaccca 154498

Query: 298    gaagatgacatatgcaagta 317
              ||||||||||||||||||||
Sbjct: 154497 gaagatgacatatgcaagta 154478


 Score =  361 bits (182), Expect = 5e-97
 Identities = 185/186 (99%)
 Strand = Plus / Minus

Query: 310    tgcaagtatgattttgtagaagttgaggaacccagtgatggaactatattagggcgctgg 369
              |||| |||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 115282 tgcaggtatgattttgtagaagttgaggaacccagtgatggaactatattagggcgctgg 115223

Query: 370    tgtggttctggtactgtaccaggaaaacagatttctaaaggaaatcaaattaggataaga 429
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 115222 tgtggttctggtactgtaccaggaaaacagatttctaaaggaaatcaaattaggataaga 115163

Query: 430    tttgtatctgatgaatattttccttctgaaccagggttctgcatccactacaacattgtc 489
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 115162 tttgtatctgatgaatattttccttctgaaccagggttctgcatccactacaacattgtc 115103

Query: 490    atgcca 495
              ||||||
Sbjct: 115102 atgcca 115097
```

>AC093325.3.1.130754
Length = 130754

Score = 236 bits (119), Expect = 2e-59
Identities = 119/119 (100%)
Strand = Plus / Minus

```
Query: 1     atgagcctcttcgggcttctcctgctgacatctgccctggccggccagagacaggggact 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 80211 atgagcctcttcgggcttctcctgctgacatctgccctggccggccagagacaggggact 80152


Query: 61    caggcggaatccaacctgagtagtaaattccagttttccagcaacaaggaacagaacgg 119
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct: 80151 caggcggaatccaacctgagtagtaaattccagttttccagcaacaaggaacagaacgg 80093
```

☐ 1: AC092608. Homo sapiens BAC ...[gi:15668121]


```
LOCUS       AC092608               196952 bp    DNA     linear   PRI 01-MAR-2002
DEFINITION  Homo sapiens BAC clone RP11-154F14 from 4, complete sequence.
ACCESSION   AC092608 AC009582
VERSION     AC092608.2  GI:15668121
KEYWORDS    HTG.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 196952)
  AUTHORS   Sulston,J.E. and Waterston,R.
  TITLE     Toward a complete human genome sequence
  JOURNAL   Genome Res. 8 (11), 1097-1108 (1998)
  MEDLINE   99063792
   PUBMED   9847074
REFERENCE   2  (bases 1 to 196952)
  AUTHORS   Isak,A., Kozlowicz,A. and Hawkins,M.
  TITLE     The sequence of Homo sapiens BAC clone RP11-154F14
  JOURNAL   Unpublished (2001)
REFERENCE   3  (bases 1 to 196952)
  AUTHORS   Waterston,R.H.
  TITLE     Direct Submission
  JOURNAL   Submitted (19-JUL-2001) Genome Sequencing Center, Washington
            University School of Medicine, 4444 Forest Park Parkway, St. Louis,
            MO 63108, USA
REFERENCE   4  (bases 1 to 196952)
  AUTHORS   Waterston,R.H.
  TITLE     Direct Submission
  JOURNAL   Submitted (19-SEP-2001) Genome Sequencing Center, Washington
            University School of Medicine, 4444 Forest Park Parkway, St. Louis,
            MO 63108, USA
REFERENCE   5  (bases 1 to 196952)
  AUTHORS   Waterston,R.
  TITLE     Direct Submission
  JOURNAL   Submitted (01-MAR-2002) Department of Genetics, Washington
            University, 4444 Forest Park Avenue, St. Louis, Missouri 63108, USA
COMMENT     On Sep 19, 2001 this sequence version replaced gi:14916193.
            -------------- Genome Center
                Center: Washington University Genome Sequencing Center
                Center code: WUGSC
                Web site: http://genome.wustl.edu/gsc
                Contact: sapiens@watson.wustl.edu
            -------------- Summary Statistics
                Center project name: H_NH0154F14
                Drafting Center: WIBR
            --------------.
```

☐ 1: AC093325. Homo sapiens BAC ...[gi:15982602]


```
LOCUS       AC093325               130754 bp    DNA     linear   PRI 09-JAN-2002
DEFINITION  Homo sapiens BAC clone RP11-612J15 from 4, complete sequence.
ACCESSION   AC093325
VERSION     AC093325.3  GI:15982602
KEYWORDS    HTG.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 130754)
  AUTHORS   Sulston,J.E. and Waterston,R.
  TITLE     Toward a complete human genome sequence
  JOURNAL   Genome Res. 8 (11), 1097-1108 (1998)
  MEDLINE   99063792
   PUBMED   9847074
REFERENCE   2  (bases 1 to 130754)
  AUTHORS   Waligorski,J. and Haakenson,W.
  TITLE     The sequence of Homo sapiens BAC clone RP11-612J15
  JOURNAL   Unpublished (2002)
REFERENCE   3  (bases 1 to 130754)
  AUTHORS   Waterston,R.H.
  TITLE     Direct Submission
  JOURNAL   Submitted (18-AUG-2001) Genome Sequencing Center, Washington
            University School of Medicine, 4444 Forest Park Parkway, St. Louis,
            MO 63108, USA
REFERENCE   4  (bases 1 to 130754)
  AUTHORS   Waterston,R.H.
  TITLE     Direct Submission
  JOURNAL   Submitted (07-OCT-2001) Genome Sequencing Center, Washington
            University School of Medicine, 4444 Forest Park Parkway, St. Louis,
            MO 63108, USA
REFERENCE   5  (bases 1 to 130754)
  AUTHORS   Waterston,R.
  TITLE     Direct Submission
  JOURNAL   Submitted (09-JAN-2002) Department of Genetics, Washington
            University, 4444 Forest Park Avenue, St. Louis, Missouri 63108, USA
COMMENT     On Oct 7, 2001 this sequence version replaced gi:15624997.
            -------------- Genome Center
                Center: Washington University Genome Sequencing Center
                Center code: WUGSC
                Web site: http://genome.wustl.edu/gsc
                Contact: sapiens@watson.wustl.edu
            -------------- Summary Statistics
                Center project name: H_NH0612J15
            --------------.

            NOTICE:  This sequence may not represent the entire insert of this
```